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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/851,628	05/06/97	COHEN C	CRF-145

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PATENT ADMINISTRATOR
TESTA HURWITZ & THIBEAULT
HIGH STREET TOWER
125 HIGH STREET
BOSTON MA 02110

EXAMINER	
ROMEO, D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/17/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/851,628	Cohen et al.
Examiner: David Romeo 8/14/98	Group Art Unit: 1646

☒ Responsive to communication(s) filed on *Nov 26, 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17, 24, 28, and 32* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17, 24, 28, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3, 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ **NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. The preliminary amendment filed 26 November 1997 (Paper No. 3) has been entered in full. Claims 1-17, 24, 28 and 32 are pending and are being examined.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by

the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-17, 24, 28 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods comprising administering a dimeric protein wherein the subunits of said dimer comprise an amino acid having at least 70% amino acid sequence homology with the C-terminal seven cysteine domain of human OP-1, residues 330-431 of SEQ ID NO:2 of U.S. Patent No. 5,266,683, and wherein said dimeric protein induces chondrogenesis in the Reddi-Sampath ectopic bone assay, does not reasonably provide enablement for the claimed methods without regard to the structural and functional characteristics of the renal therapeutic agent. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Note that a claim which recites "residues 330-431 of SEQ ID NO:2 of U.S. Patent No. 5,266,683" does not comply with the sequence rules, as noted above.

The instant specification does not identify that material element or combination of elements which is unique to and, therefore, definitive of "an OP/BMP renal therapeutic agent", "OP-1", "OP-2", "OP-3", "BMP2", "BMP3", "BMP4", "BMP5", "BMP6", "BMP9", "human osteogenic proteins and human bone morphogenetic proteins", "a C-terminal cysteine domain", and "an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1" and defines OP/BMP family members as biosynthetically produced variants of known naturally occurring proteins and as new, unknown and un-discovered, proteins (page 14, full paragraph 1). The metes and bounds of "a C-terminal cysteine domain" are not clear. The structure of a polypeptide comprising "an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1" is unlimited beyond a single amino acid of OP-1.

The claimed methods encompass using polypeptides structurally unrelated to the instantly disclosed OP-1, using polypeptides homologous to polypeptides structurally unrelated to the instantly disclosed OP-1, and using polypeptides comprising a single amino acid of the instantly disclosed polypeptides. There are no structural or functional limitations to the renal therapeutic agents used in the claimed methods. The skilled artisan is left to extensive, random, trial and error

experimentation wherein biosynthetically produced variants of undefined structure and function of known naturally occurring proteins are tested in the claimed methods. Such experimentation is considered undue. Furthermore, it is not possible to predict function from primary amino acid sequence data. See Bowie et al. (W) page 1306, column 1, full paragraph 1, wherein it is taught that predicting structure, hence function, from primary amino acid sequence data is extremely complex, and it unlikely the problem will be solved in the near future.

Furthermore, the specification only presents a single working example of a renal therapeutic agent, i.e. OP-1. It is unlikely that this single example would enable the skilled artisan to make and use renal therapeutic agents that are structurally unrelated to OP-1.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-17, 24, 28 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17, 24, 28 and 32 are indefinite because they lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved; an intended use is not the same as achieving a result; in the absence of a recitation as to any result, or a process step producing a result, it is unclear what result of the process can be inferred.

Claims 1-17, 24, 28 and 32 are indefinite because it is unclear what effect is intended by an "therapeutically effective amount"; an intended use is not the same as a therapeutic effect; in the absence of a recitation as to any therapeutic effect, or a process step producing a therapeutic effect, or a therapeutically effective amount of the agent to cause a therapeutic effect, it is unclear what therapeutic effect can be inferred.

Claims 1, 11-17, 24, 28 and 33 are indefinite because they recite the term "an OP/BMP renal therapeutic agent". Because the instant specification does not identify that material element or combination of elements which is unique to and, therefore, definitive of "an OP/BMP renal therapeutic agent" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claims 3-10 are indefinite because they recite the term "OP-1". Because the instant specification does not identify that material element or combination of elements which is unique to

and, therefore, definitive of "OP-1" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claim 3 is indefinite because it recites the terms "OP-2", "OP-3", "BMP2", "BMP3", "BMP4", "BMP5", "BMP6", and "BMP9". Because the instant specification does not identify that material element or combination of elements which is unique to and, therefore, definitive of "OP-2", "OP-3", "BMP2", "BMP3", "BMP4", "BMP5", "BMP6", and "BMP9" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of these elements.

Claim 12 is indefinite because it recites the term "human osteogenic proteins and human bone morphogenetic proteins". Because the instant specification does not identify that material element or combination of elements which is unique to and, therefore, definitive of "human osteogenic proteins and human bone morphogenetic proteins" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claims 5-11 recite the limitation "said renal therapeutic agent". There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claims recite the limitation --said OP/BMP renal therapeutic agent--.

Claims 3-4 are indefinite because they recite the term "a C-terminal cysteine domain". Because the instant specification does not identify that material element or combination of

elements which is unique to and, therefore, definitive of "a C-terminal cysteine domain" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claims 3 and 4 are indefinite over the recitation of "consisting of at least". The transitional phrase "consisting of" defines the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim and excludes any element, step, or ingredient not specified in the claim. The transitional term "at least" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps and leaves the claim open for the inclusion of unspecified ingredients even in major amounts. It is unclear whether the phrase "consisting of" limits the scope of "at least". The metes and bounds of the claim are not clearly set forth.

Claims 5-11 are indefinite because they recite the term "a C-terminal seven-cysteine domain of human OP-1". Because the instant specification does not identify that material element or combination of elements which is unique to and, therefore, definitive of "a C-terminal seven-cysteine domain of human OP-1" an artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Kuberasampath et al. (BB, cited by Applicants). Kuberasampath et al. disclose the administration of OP-1 to a mammal (paragraph bridging pages 51-52) at a dose range from about 10 ng/kg to about 1 g/kg of body weight per day (paragraph bridging pages 59-60). The instant specification discloses at page 6, full paragraph 1, that daily dosages of the renal therapeutic agents of the instant invention are in the range of about 0.01-1000 μg/kg body weight. Kuberasampath et al. disclose administering to a mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-17, 24, 28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glassock et al. (V) and Brenner et al. (U) in view of Kuberasampath et al. (BB, cited by Applicants).

Glassock et al. teach that immunologic events play an important role in many forms of renal injury (page 1292, column 1, full paragraph 1), that polymorphonuclear leukocytes, eosinophils, monocytes, macrophages, and platelets constitute the cellular mediators of renal injury, and that the activation of these cells induces the expression on the cell surface of molecules that enhance their adhesion to vascular endothelium, thus promoting their migration and localization within sites of tissue injury, and directly influencing renal hemodynamics, capillary wall permeability, and tubular function (paragraph bridging pages 1292-1293). Glassock et al. also suggest that interfering with the accumulation of the cellular mediators of renal injury may ameliorate the clinical and morphological manifestations of renal disease (paragraph bridging pages 1294-1295).

Brenner et al. teach that many forms of chronic renal injury progress inexorably to chronic renal failure (page 1274, column 1, full paragraph 1), and that conservative, i.e. non-dialytic, non-transplant, therapy of progressive renal failure is instituted to control symptoms, minimize complications, prevent long-term sequelae, and slow the progression of renal insufficiency (paragraph bridging pages 1280-1281). Brenner et al. teach that glomerulonephritis is a cause of chronic renal failure (paragraph bridging pages 1274-1275 and Figure 237-1) and that those forms

of glomerulonephritis that respond to immunosuppressive therapy should be treated aggressively (page 1281, column 1, full paragraph 1). Brenner et al. (U) teaches that in the relatively early stages of CRF the total glomerular filtration rate (GFR) is reduced to levels of about 35-50% of normal (page 1275, column 1), that differentiation between acute and chronic renal failure can be difficult and that the usual hallmark of chronic renal failure is reduced kidney size on ultrasound, abdominal scout film, or pyelogram, that in the absence of small kidneys, renal biopsy may be necessary for diagnosis (page 1276, column 2, full paragraph 4) and that dialysis therapy may cause unique abnormalities not seen prior to the initiation of therapy (paragraph bridging pages 1276-1277).

Glassock et al. and Brenner et al. do not teach a method of treatment for a mammal in, or at risk of, chronic renal failure or a method of treatment to delay the need for, or reduce the frequency of, chronic dialysis treatments, said methods comprising administering an OP/BMP renal therapeutic agent.

Kuberasampath et al. disclose alleviating the tissue destructive effects associated with the body's inflammatory response to tissue injury by modulating the attachment of immune effector cells to the luminal side of the endothelium of blood vessels at or near the site of tissue damage by administering morphogens (page 38, line 3, through page 40, line 9), disclose OP-1 is a morphogen (page 43, full paragraph 2), and disclose the administration of morphogens to an individual by any suitable means or parenterally by intra-capsular administration (page 51, lines

1-15). The instant specification discloses that intra-capsular administration is a preferred route of administration for renal therapeutic agents. See the instant specification at page 6, full paragraph 1. Kuberasampath et al. do not teach a method of treatment for a mammal in, or at risk of, chronic renal failure or a method of treatment to delay the need for, or reduce the frequency of, chronic dialysis treatments, said methods comprising administering an OP/BMP renal therapeutic agent.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that inflammation leads to renal injury, that chronic inflammation would lead to chronic renal injury, which would progress to chronic renal failure, and that anti-inflammatory therapy would ameliorate the clinical and morphological manifestations of renal disease due to inflammation. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that a mammal with glomerulonephritis is a mammal in, or at risk of, chronic renal failure, and that treating a mammal in, or at risk of, chronic renal failure, with anti-inflammatory therapy would delay the need for, or reduce the frequency of, chronic dialysis treatments. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal in, or at risk of, chronic renal failure, with anti-inflammatory therapy, as taught by Glassock et al. and Brenner et al., and to modify that teaching by treating with an anti-inflammatory amount of OP-1, as taught by Kuberasampath et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make

this modification in order to delay the onset of chronic renal failure or to treat the sequelae of chronic renal failure. Furthermore, Kuberasampath et al. recognize the suitability of morphogens for suppressing inflammation. The motivation to combine Glassock et al and Brenner et al. in view of Kuberasampath et al. arises from the expectation that anti-inflammatory therapy will delay the onset of chronic renal failure or treat the sequelae of chronic renal failure, that OP-1 is an anti-inflammatory agent, and that administering OP-1 will suppress the inflammatory reactions leading to chronic renal failure or to the sequelae of chronic renal failure. Furthermore, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable parameters by routine experimentation.

The invention is prima facie obvious over the prior art.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the Examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

DSR DSR
August 15, 1998